UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/627,787 | 07/27/2000 | Eugen Uhlmann | 02481.1679 | 1128 |

5487 7590 10/03/2006

ROSS J. OEHLER
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |
| ART UNIT | PAPER NUMBER |
| 1635 | |

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/627,787 | UHLMANN ET AL. | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *9 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Attached pages 9 & 10

## DETAILED ACTION

An amendment was received on 7/24/06. Claims 8 and 10-36 were canceled as requested. Claims 9 and 37-39 remain pending. Previously these claims were indicated to contain allowable subject matter. After further search and consideration this indication is withdrawn. The Examiner regrets the error.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (J. Biol. Chem. 268(21): 15812-22, 1993).

Chen taught fluorescent probes for protein kinase C activity that are identical in structure to instant structure F1. See e.g. Fig. 1, panel B, structures 6 and 7, on page 15814, and also the attached search result. The conjugates are considered to be both pharmaceutical and diagnostic compositions, as required by instant claims 37 and 38, because they satisfy all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Laurent et al (Bioconj. Chem. 8: 856-861, 1997).

Laurent taught instantly claimed conjugate F2 wherein an oligonucleotide was linked by an esterase-sensitive bond to the fluorescein derivative of instant F2. See Scheme 1 on page 858. The conjugate was microinjected into cells in culture. See e.g. Fig. 4 on page 859. The conjugate that was microinjected into the cultured cells is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims. Although the structure in scheme 1 on page 859 does not specify the atom of the aryl ring to which the conjugate-carrying ester group is attached, under the synthesis protocol followed, the products recovered would include the claimed compound absent evidence to the contrary.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Limberg et al (Liebigs Ann. 11:1773-1784, 1996).

Limberg taught conjugates for assaying sialyltransferase activity, wherein the conjugates satisfy the structural limitations of instant structure F3 (i.e. a conjugate of carboxyfluorescein). The "molecule capable of being transported" is a disaccharide. See structure 5 in Fig. 2 on page 1774. The conjugate is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,405,746.

The '746 patent disclosed a compound embraced by instant structure F5 wherein the molecule capable of being transported is the hydroxyl group of the carboxylic acid functional group. Specifically, the search result indicates that the patent discloses a compound with the Registry No. 164256-07-9, the structure of which is shown the attached search result. The common name of the compound is 5-carboxynaphtho-fluorescein diacetate, and it is disclosed at column 12, line 44 and in claim 11 at column 44, lines 61 and 62. These passages also disclose 5 carboxyfluorescein diacetate (column 12, line 40, and column 44, line 57) which is embraced by structure F1. The conjugate is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al (J. Pharm. Exp. Ther. 286(1): 1998).

Takeuchi taught an aspirin derivative embraced by instant structure F6. See Fig. 1, bottom structure. The conjugate is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohsako et al (Biol. Pharm. Bull. 18(2): 310-314, 1995).

Ohsako taught a conjugate embraced by instant structure F7. See Table 1 on page 312, specifically pAcOHBA, wherein R1 is OH and R4 is OCOCH3. The "molecule capable of being transported" would be CH3. The conjugate is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Cohen et al (Phytochem. Anal. 2: 60-64, 1991).

Cohen taught a conjugate embraced by instant structure F8, i.e. Acetoxycoumarin-3-carboxylic acid. See structure 2 on page 61. The molecule capable of being transported is considered to be the hydroxyl group of the carboxylic acid functional group. The conjugate is considered to be both a pharmaceutical composition and a diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

Claims 9, 37, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al (Macromolecules 29: 1874-1879, 1996).

Williams taught a conjugate embraced by instant structure F9, i.e. 6-acetoxy-2-naphthoic acid (i.e. 2-naphthalenecarboxylic acid, 6-(actyloxy)-, wherein the molecule capable of being delivered is a hydroxy group on the carboxylic acid moiety. See title. The conjugate is considered to be both a pharmaceutical composition and a diagnostic

composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Chen et al (J. Biol. Chem. 268(21): 15812-22, 1993), Laurent et al (Bioconj. Chem. 8: 856-861, 1997), Limberg et al (Liebigs Ann. 11:1773-1784, 1996), US Patent 5,405,746, Takeuchi et al (J. Pharm. Exp. Ther. 286(1): 1998), Ohsako et al (Biol. Pharm. Bull. 18(2): 310-314, 1995), Cohen et al (Phytochem. Anal. 2: 60-64, 1991), or Williams et al (Macromolecules 29: 1874-1879, 1996).

The teachings of these references are discussed above, and each anticipates claim 9. None teaches a kit as required by claim 39. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the conjugates disclosed in these references into a kit because one of ordinary skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Claims 9 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Limberg et al (Liebigs Ann. 11:1773-1784, 1996) in view of (Abe et al (Applied Env. Microbiol. 64(3): 1139-1142, 1998).

Limberg taught conjugates for assaying sialyltransferase activity, wherein the conjugates satisfy the structural limitations of instant structure F3 (i.e. a conjugate of carboxyfluorescein). The "molecule capable of being transported" is a disaccharide. See structure 5 in Fig. 2 on page 1774.

Limberg did not teach a conjugate of carboxydichlorofluorescein.

Abe taught that carboxyfluorescein and carboxydichlorofluorescein were both fluorescent dyes useful for intracellular diagnostics. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute carboxydichlorofluorescein for carboxyfluorescein in the invention of Limberg. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). The conjugate would be considered to be both a pharmaceutical and diagnostic composition, as required by instant claims 37 and 38, because it satisfies all of the structural limitations of these claims.

As noted above, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the conjugate disclosed Limberg or Abe into a kit

because one of ordinary skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635

ATTACHMENT FOR CHEN REFERENCE

L6 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:576457 CAPLUS Full-text
DOCUMENT NUMBER: 119:176457
TITLE: New fluorescent probes for protein kinase C. Synthesis, characterization, and application
AUTHOR(S): Chen, Chii Shiarng; Poenie, Martin
CORPORATE SOURCE: Dep. Zool., Univ. Texas, Austin, TX, 78712, USA
SOURCE: Journal of Biological Chemistry (1993), 268(21), 15812-22
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

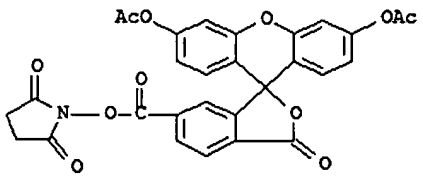
AB Fluorescent derivs. of the bisindolylmaleimide inhibitors of protein kinase C (PKC) were synthesized and tested with respect to their inhibitory potency, specificity, and usefulness as fluorescent cytol. stains for PKC. Several of the fluorescent bisindolylmaleimide derivs. (fim-1, fim-2, and rim-1) acted as ATP-competitive catalytic site inhibitors and retained much of the potency and specificity of the parental compd. The R6-C1 and the PKC.beta.1-overexpressing R6-PCK3 cell lines were used for testing fim-1 and rim-1 as cytol. strains for PKC. Comparisons showed that the R6-PCK3 cells stained much more brightly than R6-C1 cells. When R6-PKC3 cells were treated with the phorbol ester phorbol 12-myristate 13-acetate (PMA) for 30 min, staining with fim-1 or anti-PKC.beta.1 revealed a dramatic translocation of PKC to the cell periphery. When R6-PKC3 cells were exposed to PMA for 24 h to down-regulate PKC, cytoplasmic staining was drastically reduced. Staining patterns obtained with an antibody specific for PKC.beta.1 and with fim-1 were remarkably similar except for mitochondrial staining, which was only seen with fim-1. A closer examn. of the mitochondrial staining showed that mitochondria convert from filamentous to punctate shapes and cluster around the nucleus when cells are treated with PMA. This punctate morphol., perinuclear clustering, and staining with fim-1 persists when PKC is down-regulated. Overall, these results indicate that fim-1 and rim-1 can serve as useful fluorescent probes for PKC. The mitochondrial staining may be due to a PKC isoform resistant to downregulation.

CC 7-3 (Enzymes)
Section cross-reference(s): 27

IT 150206-05-6P 150206-15-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction with bisindolylmaleimide derivs.)

IT 150206-15-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction with bisindolylmaleimide derivs.)

RN 150206-15-8 CAPLUS
CN 2,5-Pyrrolidinedione, 1-[[[3',6'-bis(acetyloxy)-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-6-yl]carbonyl]oxy]- (9CI) (CA INDEX NAME)



Attachment for US Patent 5,405,746 which discloses instant structure F5.

RN 164256-07-9 REGISTRY
ED Entered STN: 30 Jun 1995
CN Spiro[7H-dibenzo[c,h]xanthene-7,1'(3'H)-isobenzofuran]-5'-carboxylic acid, 3,11-bis(acetyloxy)-3'-oxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Carboxynaphthofluorescein diacetate
FS 3D CONCORD
MF C33 H20 O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL